

=> d.his - full

(FILE 'HOME' ENTERED AT 13:48:37 ON 26 OCT 2005)

SET SFIELD BI

FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:49:06 ON 26 OCT 2005

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L1      13 SEA ABB=ON  PLU=ON  (PIPKI OR PIPK) (3A) 661
L2      458 SEA ABB=ON  PLU=ON  PHOSPHATIDYLINOSITOL PHOSPHATE (2W) KINASE
L3      16 SEA ABB=ON  PLU=ON  L2 AND 661
L4      16 SEA ABB=ON  PLU=ON  L1 OR L3
L5      133994 SEA ABB=ON  PLU=ON  CELL (3A) MIGRAT?
L6      7 SEA ABB=ON  PLU=ON  L4 AND L5
L7      24 SEA ABB=ON  PLU=ON  L2 AND L5
L8      14 SEA ABB=ON  PLU=ON  L7 AND (SRC OR FAK OR MODULAT? OR ADHESI?)
L9      14 SEA ABB=ON  PLU=ON  L6 OR L8
L10     9 DUP REM L9 (5 DUPLICATES REMOVED)
        ANSWERS '1-5' FROM FILE CAPLUS
        ANSWERS '6-7' FROM FILE EMBASE
        ANSWERS '8-9' FROM FILE BIOSIS
        D SCAN TI
L11     37 SEA ABB=ON  PLU=ON  (PIPKI OR PIPK) (3A) GAMMA
L12     23 SEA ABB=ON  PLU=ON  L11 AND (SRC OR FAK OR MODULAT? OR
        ADHESI?)
L13     18 SEA ABB=ON  PLU=ON  L12 NOT L10
L14     16 DUP REM L13 L10 (11 DUPLICATES REMOVED)
        ANSWERS '1-8' FROM FILE CAPLUS
        ANSWER '9' FROM FILE MEDLINE
        ANSWER '10' FROM FILE EMBASE
        ANSWERS '11-16' FROM FILE BIOSIS

L15     25867 SEA ABB=ON  PLU=ON  ANDERSON R?/AU
L16     950 SEA ABB=ON  PLU=ON  LING K?/AU
L17     21 SEA ABB=ON  PLU=ON  DOUGHMAN R?/AU
L18     26801 SEA ABB=ON  PLU=ON  (L15 OR L16 OR L17)
L19     74 SEA ABB=ON  PLU=ON  L18 AND (L1 OR L2 OR L11)
L20     14 SEA ABB=ON  PLU=ON  L19 AND (L1 OR L11)
L21     74 SEA ABB=ON  PLU=ON  L18 AND L2
L22     26 SEA ABB=ON  PLU=ON  L21 AND (SRC OR FAK OR MODULAT? OR ADHES?)
L23     26 SEA ABB=ON  PLU=ON  L20 OR L22
L24     13 DUP REM L23 (13 DUPLICATES REMOVED)
        ANSWERS '1-8' FROM FILE CAPLUS
        ANSWERS '9-13' FROM FILE BIOSIS
L25     3 SEA ABB=ON  PLU=ON  L24 NOT L14

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=> fil caplus medline embase biosis
FILE 'CAPLUS' ENTERED AT 13:53:59 ON 26 OCT 2005
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=> d que l14

L1 13 SEA (PIPKI OR PIPK) (3A) 661
L2 458 SEA PHOSPHATIDYLINOSITOL PHOSPHATE (2W) KINASE
L3 16 SEA L2 AND 661
L4 16 SEA L1 OR L3
L5 133994 SEA CELL (3A) MIGRAT?
L6 7 SEA L4 AND L5
L7 24 SEA L2 AND L5
L8 14 SEA L7 AND (SRC OR FAK OR MODULAT? OR ADHESI?)
L9 14 SEA L6 OR L8
L10 9 DUP REM L9 (5 DUPLICATES REMOVED)
L11 37 SEA (PIPKI OR PIPK) (3A) GAMMA
L12 23 SEA L11 AND (SRC OR FAK OR MODULAT? OR ADHESI?)
L13 18 SEA L12 NOT L10
L14 16 DUP REM L13 L10 (11 DUPLICATES REMOVED)

=> d

L14 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1
AN 2005:536221 CAPLUS
DN 143:188973
TI Phosphatidylinositol Phosphate Kinase Type Iγ Directly Associates
with and Regulates Shp-1 Tyrosine Phosphatase
AU Bairstow, Shawn F.; Ling, Kun; Anderson, Richard A.
CS Department of Pharmacology, University of Wisconsin Medical School,
Madison, WI, 53706, USA
SO Journal of Biological Chemistry (2005), 280(25), 23884-23891
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d .ca l14 1-8;d ibib ab ct l14 9-16

L14 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2005:536221 CAPLUS
DOCUMENT NUMBER: 143:188973
TITLE: Phosphatidylinositol Phosphate Kinase Type Iγ
Directly Associates with and Regulates Shp-1 Tyrosine
Phosphatase
AUTHOR(S): Bairstow, Shawn F.; Ling, Kun; Anderson, Richard A.

CORPORATE SOURCE: Department of Pharmacology, University of Wisconsin
Medical School, Madison, WI, 53706, USA

SOURCE: Journal of Biological Chemistry (2005), 280(25),
23884-23891
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular
Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 22 Jun 2005

AB Tyrosine phosphorylation plays a critical role in many regulatory aspects of
cellular signaling, and dephosphorylation of phosphotyrosine residues is
crucial for termination of signals initiated by tyrosine kinases.
Previous work has shown that the tyrosine kinase **Src**
phosphorylates Tyr644 on phosphatidylinositol phosphate kinase type I (**PIPKI**) γ 661 in a focal **adhesion**
kinase-dependent manner. Phosphorylation of this residue is essential for
high affinity binding of **PIPKI** γ 661 to the focal
adhesion protein talin and for targeting of **PIPKI**.
gamma.661 to focal **adhesions**. A yeast two-hybrid screen
performed with the C-terminal 178-amino acid tail of **PIPKI**.
gamma.661 identified an interaction with the phosphatase domain of
the tyrosine phosphatase Shp-1. The interaction between **PIPKI**.
gamma.661 and Shp-1 was confirmed via co-immunopptn. from HEK293
cell lysates. In addition, **Src**-phosphorylated **PIPKI**.
gamma.661 is a substrate for Shp-1, and Shp-1 **modulates**
both the association between **PIPKI** γ 661 and talin and
the targeting of **PIPKI** γ 661 to focal
adhesions in mammalian cells. Finally, the authors showed that
Shp-1 phosphatase activity is inhibited by the product of **PIPKI**.
gamma.661, phosphatidylinositol 4,5-bisphosphate, in vitro. These
combined results suggest a model in which the reciprocal actions of
Src tyrosine kinase and Shp-1 tyrosine phosphatase dynamically
regulate the association between **PIPKI** γ 661 and
talin.

CC 7-3 (Enzymes)
Section cross-reference(s): 13

IT Cell junction
(focal contact; phosphatidylinositol phosphate kinase type I γ
binding and regulation of tyrosine phosphatase Shp-1 in relation to **FAK**
kinase-dependent talin binding and kinase targeting to
focal **adhesions**)

IT Human
Molecular association
(phosphatidylinositol phosphate kinase type I γ binding and
regulation of tyrosine phosphatase Shp-1 in relation to **FAK**
kinase-dependent talin binding and kinase targeting to focal
adhesions)

IT Talin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(phosphatidylinositol phosphate kinase type I γ binding and
regulation of tyrosine phosphatase Shp-1 in relation to **FAK**
kinase-dependent talin binding and kinase targeting to focal
adhesions)

IT 59977-48-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(I γ ; phosphatidylinositol phosphate kinase type I γ binding
and regulation of tyrosine phosphatase Shp-1 in relation to **FAK**
kinase-dependent talin binding and kinase targeting to focal
adhesions)

IT 300855-77-0, Protein tyrosine phosphatase Shp-1
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (phosphatidylinositol phosphate kinase type I γ binding and
 regulation of tyrosine phosphatase Shp-1 in relation to **FAK**
 kinase-dependent talin binding and kinase targeting to focal
adhesions)
 IT 144114-16-9, Focal **adhesion** kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (tyrosine phosphatase Shp-1 inhibition by phosphatidylinositol
 bisphosphate in relation to phosphatidylinositol phosphate kinase
 I γ)
 REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
 ACCESSION NUMBER: 2005:168211 CAPLUS
 DOCUMENT NUMBER: 142:406442
 TITLE: Structural Basis for Phosphatidylinositol Phosphate
 Kinase Type I γ Binding to Talin at Focal
Adhesions
 AUTHOR(S): de Pereda, Jose M.; Wegener, Kate L.; Santelli,
 Eugenio; Bate, Neil; Ginsberg, Mark H.; Critchley,
 David R.; Campbell, Iain D.; Liddington, Robert C.
 CORPORATE SOURCE: Program on Cell Adhesion, Burnham Institute, La Jolla,
 CA, 92037, USA
 SOURCE: Journal of Biological Chemistry (2005), 280(9),
 8381-8386
 CODEN: JBCHA3; ISSN: 0021-9258
 PUBLISHER: American Society for Biochemistry and Molecular
 Biology
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 ED Entered STN: 28 Feb 2005
 AB The cytoskeletal protein talin binds to a short C-terminal sequence in
 phosphatidylinositol phosphate kinase type I γ (**PIPKI γ**), activating the enzyme and promoting the
 local production of phosphatidylinositol 4,5 bisphosphate, which regulates
 focal **adhesion** dynamics as well as clathrin-mediated endocytosis
 in neuronal cells. Here we show by crystallog., NMR, and calorimetric
 anal. that the phosphotyrosine binding (PTB)-like domain of talin engages
 the **PIPKI γ** C terminus in a mode very similar to
 that of integrin binding. However, **PIPKI γ** binds
 in the canonical PTB-peptide mode with an SPLH motif replacing the classic
 NPXY motif. The tighter packing of the SPLH motif against the hydrophobic
 core of talin may explain the stronger binding of **PIPKI γ** .
gamma.. Two tyrosine residues flanking the SPLH motif (Tyr-644
 and Tyr-649) have been implicated in the regulation of talin binding. We
 show that phosphorylation at Tyr-644, a **Src** phosphorylation site
 in vivo, has little effect on the binding mode or strength, which is
 consistent with modeling studies in which the phosphotyrosine makes
 surface-exposed salt bridges, and we suggest that its strong activating
 effect arises from the release of autoinhibitory restraints in the
 full-length **PIPKI γ** . Modeling studies suggest
 that phosphorylation of Tyr-649 will likewise have little effect on talin
 binding, whereas phosphorylation of the SPLH serine is predicted to be
 strongly disruptive. Our data are consistent with the proposal that
Src activity promotes a switch from integrin binding to
PIPKI γ binding that regulates focal
adhesion turnover.
 CC 7-3 (Enzymes)

Section cross-reference(s): 13, 75

ST crystal structure phosphatidylinositol phosphate kinase Igamma talin focal **adhesion**

IT Talin
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
 (FERM F3 domain of, fusion with a phosphatidylinositol phosphate kinase Iy fragment; structural basis for phosphatidylinositol phosphate kinase type Iy binding to talin at focal **adhesions**)

IT Cell junction
 (focal contact; structural basis for phosphatidylinositol phosphate kinase type Iy binding to talin at focal **adhesions**)

IT Phosphorylation, biological
 (protein; **Src** activity promotes a switch from integrin binding to **PIPKIy** binding that regulates focal **adhesion** turnover)

IT Conformation
 (protein; structural basis for phosphatidylinositol phosphate kinase type Iy binding to talin at focal **adhesions**)

IT Molecular association
 Molecular recognition
 (structural basis for phosphatidylinositol phosphate kinase type Iy binding to talin at focal **adhesions**)

IT 141349-89-5, **Src** tyrosine kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (**Src** activity promotes a switch from integrin binding to **PIPKIy** binding that regulates focal **adhesion** turnover)

IT 59977-48-9D, Iy, fragment of, fusion with talin FERM F3 domain
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
 (structural basis for phosphatidylinositol phosphate kinase type Iy binding to talin at focal **adhesions**)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2005:207606 CAPLUS

DOCUMENT NUMBER: 142:237160

TITLE: Regulation of the interaction between PIPKIy and talin by proline-directed protein kinases

AUTHOR(S): Lee, Sang Yoon; Voronov, Sergey; Letinic, Kresimir; Nairn, Angus C.; Di Paolo, Gilbert; De Camilli, Pietro

CORPORATE SOURCE: Howard Hughes Medical Institute and Department of Cell Biology, Yale University School of Medicine, New Haven, CT, 06510, USA

SOURCE: Journal of Cell Biology (2005), 168(5), 789-799
 CODEN: JCLBA3; ISSN: 0021-9525

PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 09 Mar 2005

AB The interaction of talin with phosphatidylinositol(4) phosphate 5 kinase type Iy (PIPKIy) regulates PI(4,5)P2 synthesis at synapses and at focal **adhesions**. Here, we show that phosphorylation of serine 650 (S650) within the talin-binding sequence of human PIPKIy blocks this interaction. At synapses, S650 is phosphorylated by p35/Cdk5 and mitogen-activated protein kinase at rest, and dephosphorylated by calcineurin upon stimulation. S650 is also a substrate for cyclin B1/Cdk1 and its phosphorylation in mitosis correlates with focal **adhesion**

disassembly. Phosphorylation by **Src** of the tyrosine adjacent to S650 (Y649 in human PIPKI γ) was shown to enhance PIPKI γ targeting to focal **adhesions**. We find that Y649 phosphorylation does not stimulate directly PIPKI γ binding to talin, but may do so indirectly by inhibiting S650 phosphorylation. Conversely, S650 phosphorylation inhibits Y649 phosphorylation by **Src**. The opposite effects of the phosphorylation of Y649 and S650 likely play a critical role in regulating synaptic function as well as the balance between cell **adhesion** and cell motility.

CC 13-6 (Mammalian Biochemistry)

Section cross-reference(s): 6

ST **phosphatidylinositol phosphate kinase** serine

phosphorylation Cdk5 talin assocn synapse; PIPKI γ tyrosine

phosphorylation **src** kinase focal **adhesion** fibroblast;

ERK1 ERK2 kinase calcineurin PIPKI γ dephosphorylation **cell**

adhesion migration; cyclin B1 Cdk1 kinase PIPKI γ

phosphorylation mitosis

IT Molecular association

(PIPKI γ - talin; regulation of interaction between human

PIPKI γ and talin by PIPKI γ phosphorylation induced by

proline-directed protein kinases in synapses in relation to cell cycle,

adhesion, and motility)

IT Dephosphorylation, biological

(PIPKI γ , by calcineurin; regulation of interaction between human

PIPKI γ and talin by PIPKI γ phosphorylation induced by

proline-directed protein kinases in synapses in relation to cell cycle,

adhesion, and motility)

IT Cell junction

(focal contact, PIPKI γ targeting to; regulation of interaction

between human PIPKI γ and talin by PIPKI γ phosphorylation

induced by proline-directed protein kinases in synapses in relation to

cell cycle, **adhesion**, and motility)

IT Biological transport

(intracellular, PIPKI γ ; regulation of interaction between human

PIPKI γ and talin by PIPKI γ phosphorylation induced by

proline-directed protein kinases in synapses in relation to cell cycle,

adhesion, and motility)

IT Protein motifs

(phosphorylation site, Ser-650 in talin-binding sequence of

PIPKI γ ; regulation of interaction between human PIPKI γ and

talin by PIPKI γ phosphorylation induced by proline-directed

protein kinases in synapses in relation to cell cycle, **adhesion**

, and motility)

IT Protein motifs

(phosphorylation site, Y649 in PIPKI γ ; regulation of interaction

between human PIPKI γ and talin by PIPKI γ phosphorylation

induced by proline-directed protein kinases in synapses in relation to

cell cycle, **adhesion**, and motility)

IT Phosphorylation, biological

(protein, PIPKI γ ; regulation of interaction between human

PIPKI γ and talin by PIPKI γ phosphorylation induced by

proline-directed protein kinases in synapses in relation to cell cycle,

adhesion, and motility)

IT **Adhesion**, biological

Cell migration

Fibroblast

Human

Mitosis

Synapse

(regulation of interaction between human PIPKI γ and talin by

PIPKI γ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

- IT Talin
RL: BSU (Biological study, unclassified); BIOL (Biological study) (regulation of interaction between human PIPKI γ and talin by PIPKI γ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)
- IT Organelle
(stress fiber; regulation of interaction between human PIPKI γ and talin by PIPKI γ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)
- IT 361540-77-4, Calcineurin
RL: BSU (Biological study, unclassified); BIOL (Biological study) (PIPKI γ dephosphorylation by; regulation of interaction between human PIPKI γ and talin by PIPKI γ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)
- IT 137632-07-6, ERK1 kinase 137632-08-7, ERK2 kinase 146702-82-1, Cyclin B1-Cdc2 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (PIPKI γ phosphorylation by; regulation of interaction between human PIPKI γ and talin by PIPKI γ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)
- IT 56-45-1, L-Serine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Ser-650, Cdk5 phosphorylation site in PIPKI γ ; regulation of interaction between human PIPKI γ and talin by PIPKI γ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)
- IT 60-18-4, L-Tyrosine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Y649, **Src** phosphorylation site in PIPKI γ ; regulation of interaction between human PIPKI γ and talin by PIPKI γ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)
- IT 144697-17-6, Gene c-**src** kinase 147014-96-8, CDK5 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (regulation of interaction between human PIPKI γ and talin by PIPKI γ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)
- IT 104645-76-3, Phosphatidylinositol(4) phosphate 5 kinase
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study) (type I γ ; regulation of interaction between human PIPKI γ and talin by PIPKI γ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2004:1715 CAPLUS
DOCUMENT NUMBER: 140:124315
TITLE: Tyrosine phosphorylation of type I γ phosphatidylinositol phosphate

kinase by **Src** regulates an integrin-talin switch

AUTHOR(S): Ling, Kun; Doughman, Renee L.; Iyer, Vidhya V.; Firestone, Ari J.; Bairstow, Shawn F.; Mosher, Deane F.; Schaller, Michael D.; Anderson, Richard A.

CORPORATE SOURCE: Department of Pharmacology, Program in Molecular and Cellular Pharmacology, University of Wisconsin Medical School, Madison, WI, 53706, USA

SOURCE: Journal of Cell Biology (2003), 163(6), 1339-1349
CODEN: JCLBA3; ISSN: 0021-9525

PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 02 Jan 2004

AB Engagement of integrin receptors with the extracellular matrix induces the formation of focal **adhesions** (FAs). Dynamic regulation of FAs is necessary for **cells** to polarize and **migrate**. Key interactions between FA scaffolding and signaling proteins are dependent on tyrosine phosphorylation. However, the precise role of tyrosine phosphorylation in FA development and maturation is poorly defined. Here, we show that phosphorylation of type I γ **phosphatidylinositol phosphate kinase** (**PIPKI.gamma.661**) on Tyr644 residue is critical for its interaction with talin, and consequently, localization to FAs. **PIPKI.gamma.661** is specifically phosphorylated on Y644 by **Src**. Phosphorylation is regulated by focal **adhesion** kinase, which enhances the association between **PIPKI.gamma.661** and **Src**. The phosphorylation of Y644 results in an .apprx.15-fold increase in binding affinity to the talin head domain and blocks β -integrin binding to talin. This defines a novel phosphotyrosine-binding site on the talin F3 domain and a "mol. switch" for talin binding between **PIPKI.gamma.661** and β -integrin that may regulate dynamic FA turnover.

CC 6-3 (General Biochemistry)
Section cross-reference(s): 7

ST tyrosine phosphorylation **phosphatidylinositol phosphate kinase src** integrin talin

IT Signal transduction, biological
(Tyr644 residue phosphorylation of type I γ **phosphatidylinositol phosphate kinase** by **Src** kinase regulates integrin-talin switch)

IT Integrins
Phosphatidylinositol 4,5-bisphosphate
Talin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Tyr644 residue phosphorylation of type I γ **phosphatidylinositol phosphate kinase** by **Src** kinase regulates integrin-talin switch)

IT Cell junction
(focal contact; Tyr644 phosphorylation regulates **phosphatidylinositol phosphate kinase**-talin association and focal contact targeting of **phosphatidylinositol phosphate kinase**)

IT Phosphorylation, biological
(protein; Tyr644 residue phosphorylation of type I γ **phosphatidylinositol phosphate kinase** by **Src** kinase regulates integrin-talin switch)

IT Protein motifs
(talin head domain; Tyr644 residue phosphorylation of type I γ **phosphatidylinositol phosphate kinase** by

Src kinase regulates integrin-talin switch)
 IT 56-87-1, L-Lysine, biological studies 74-79-3, L-Arginine, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (Lys357 and Arg358 residues of talin promote its binding to phosphorylated **phosphatidylinositol phosphate kinase**)
 IT 60-18-4, L-Tyrosine, biological studies 59977-48-9 141349-89-5, Gene **src** kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (Tyr644 residue phosphorylation of type Iy **phosphatidylinositol phosphate kinase** by **Src** kinase regulates integrin-talin switch)
 IT 80449-02-1, Nonreceptor tyrosine kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (c-**Src** association with **phosphatidylinositol phosphate kinase** is enhanced by nonreceptor tyrosine kinase)
 REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 6
 ACCESSION NUMBER: 2002:844588 CAPLUS
 DOCUMENT NUMBER: 138:268816
 TITLE: Type Iy phosphatidylinositol phosphate kinase targets and regulates focal **adhesions**
 AUTHOR(S): Ling, Kun; Doughman, Renee L.; Firestone, Ari J.; Bunce, Matthew W.; Anderson, Richard A.
 CORPORATE SOURCE: Department of Pharmacology, Program in Molecular and Cellular Pharmacology, University of Wisconsin Medical School, University of Wisconsin-Madison, Madison, WI, 53706, USA
 SOURCE: Nature (London, United Kingdom) (2002), 420(6911), 89-93
 CODEN: NATUAS; ISSN: 0028-0836
 PUBLISHER: Nature Publishing Group
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 ED Entered STN: 07 Nov 2002
 AB The ability of cells to form cell contacts, adhere to the extracellular matrix, change morphol., and migrate is essential for development, wound healing, metastasis, cell survival and the immune response. These events depend on the binding of integrin to the extracellular matrix, and assembly of focal **adhesions**, which are complexes comprising scaffolding and signalling proteins organized by **adhesion** to the extracellular matrix. Phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P2) regulates interactions between these proteins, including the interaction of vinculin with actin and talin. The binding of talin to β -integrin is strengthened by PtdIns(4,5)P2, suggesting that the basis of focal **adhesion** assembly is regulated by this lipid mediator. Here we show that the type I phosphatidylinositol phosphate kinase isoform- γ 661 (**PIPKI.gamma** .661), an enzyme that makes PtdIns(4,5)P2, is targeted to focal **adhesions** by an association with talin. **PIPKI.gamma** .661 is tyrosine phosphorylated by focal **adhesion** associated kinase signalling, increasing both the activity of phosphatidylinositol phosphate kinase and its association with talin. This defines a mechanism for spatial generation of PtdIns(4,5)P2 at focal **adhesions**.
 CC 13-2 (Mammalian Biochemistry)
 ST phosphatidylinositol phosphate kinase type I talin focal **adhesion**

IT Cell junction
(focal contact; type I γ phosphatidylinositol phosphate kinase targets and regulates focal **adhesions** through association with talin)

IT Molecular association
(type I γ phosphatidylinositol phosphate kinase targets and regulates focal **adhesions** through association with talin)

IT Phosphatidylinositol 4,5-bisphosphate
Talin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type I γ phosphatidylinositol phosphate kinase targets and regulates focal **adhesions** through association with talin)

IT 104645-76-3, Phosphatidylinositol 4-phosphate 5-kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type I γ phosphatidylinositol phosphate kinase targets and regulates focal **adhesions** through association with talin)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:430584 CAPLUS

DOCUMENT NUMBER: 143:4780

TITLE: The LIM protein Ajuba regulates phosphatidylinositol 4,5-bisphosphate levels in **migrating cells** through an interaction with and activation of PIPKI α

AUTHOR(S): Kisseleva, Marina; Feng, Yungfeng; Ward, Michael; Song, Chunhua; Anderson, Richard A.; Longmore, Gregory D.

CORPORATE SOURCE: Departments of Medicine and Cell Biology, Washington University, St. Louis, MO, USA

SOURCE: Molecular and Cellular Biology (2005), 25(10), 3956-3966
CODEN: MCEBD4; ISSN: 0270-7306

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 20 May 2005

AB The phosphoinositide phosphatidylinositol 4,5-bisphosphate [PI(4,5)P₂] regulates the activity of many actin-binding proteins and as such is an important **modulator** of cytoskeleton organization during **cell migration**, for example. In **migrating cells** actin remodeling is tightly regulated and localized; therefore, how the PI(4,5)P₂ level is spatially and temporally regulated is crucial to understanding how it controls **cell migration**. Here we show that the LIM protein Ajuba contributes to the cellular regulation of PI(4,5)P₂ levels by interacting with and activating the enzymic activity of the PI(4)P 5-kinase (PIPKI α), the predominant enzyme in the synthesis of PI(4,5)P₂, in a migration stimulus-regulated manner. In migrating primary mouse embryonic fibroblasts (MEFs) from Ajuba^{-/-} mice the level of PI(4,5)P₂ was decreased with a corresponding increase in the level of the substrate PI(4)P. Reintroduction of Ajuba into these cells normalized PI(4,5)P₂ levels. Localization of PI(4,5)P₂ synthesis and PIPKI α in the leading lamellipodia and membrane ruffles, resp., of migrating Ajuba^{-/-} MEFs was impaired. In vitro, Ajuba dramatically activated the enzymic activity of PIPKI α while inhibiting the activity of PIPKI β . Thus, in addition to its effects upon Rac activity Ajuba can also influence **cell migration** through regulation of PI(4,5)P₂ synthesis through direct activation of PIPKI α enzyme activity.

CC 13-6 (Mammalian Biochemistry)
 ST Ajuba PIPKI assocn phosphatidylinositol bisphosphate formation
**cell migration; phosphatidylinositol
 phosphate kinase Ajuba cell migration**
 IT Molecular association
 (Ajuba with PIPKI α and PIPKII β ; LIM protein Ajuba regulates
 phosphatidylinositol 4,5-bisphosphate levels in **migrating
 cells** through interaction with and activation of PIPKI α)
 IT Proteins
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (LIM domain-containing, Ajuba; LIM protein Ajuba regulates
 phosphatidylinositol 4,5-bisphosphate levels in **migrating
 cells** through interaction with and activation of PIPKI α)
 IT **Cell migration**
 Human
 (LIM protein Ajuba regulates phosphatidylinositol 4,5-bisphosphate
 levels in **migrating cells** through interaction with
 and activation of PIPKI α)
 IT Phosphatidylinositol 4,5-bisphosphate
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (LIM protein Ajuba regulates phosphatidylinositol 4,5-bisphosphate
 levels in **migrating cells** through interaction with
 and activation of PIPKI α)
 IT Cell membrane
 (PIPKI α in; LIM protein Ajuba regulates phosphatidylinositol
 4,5-bisphosphate levels in **migrating cells** through
 interaction with and activation of PIPKI α)
 IT Organelle
 (lamellipodium, PI(4,5)P2 in; LIM protein Ajuba regulates
 phosphatidylinositol 4,5-bisphosphate levels in **migrating
 cells** through interaction with and activation of PIPKI α)
 IT 104645-76-3, Phosphatidylinositol-4-phosphate 5-kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (I α and II β ; LIM protein Ajuba regulates
 phosphatidylinositol 4,5-bisphosphate levels in **migrating
 cells** through interaction with and activation of PIPKI α)
 REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:1873 CAPLUS
 DOCUMENT NUMBER: 142:89354
 TITLE: Methods for identifying agents **modulating**
 activity of **PIPKI.gamma.661** for
 preventing or treating **cell-
 migration** mediated conditions or diseases
 INVENTOR(S): Anderson, Richard A.; Ling, Kun; Doughman, Renee L.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 47 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004265295	A1	20041230	US 2003-606038	20030625
PRIORITY APPLN. INFO.:			US 2003-606038	20030625
ED Entered STN:		31 Dec 2004		

- AB The present invention relates to methods of identifying agents that **modulates** the activity of type I **phosphatidylinositol phosphate kinase** isoform .gamma.661 (**PIPKI.gamma.661**) and methods of using such agents to prevent or treat a **cell migration**-mediated condition or disease in a subject are also provided. Specifically, the method involves contacting **PIPKI.gamma.661** with a test agent in the presence of at least one selected protein and detecting the activity of **PIPKI.gamma.661**, a change in the activity of **PIPKI.gamma.661** as compared to a control is indicative of said agent **modulating** the activity of **PIPKI661**. In one preferred embodiment, the agent **modulates** the activity of **Src** or **FAK** thereby **modulating** the activity of **PIPKI.gamma.661**. The present invention also relates to a method for identifying an agent that **modulates** cell focal **adhesion** assembly.
- IC ICM G01N033-53
ICS G01N033-567; A61K038-48
- INCL 424094500; 435007200
- CC 9-2 (Biochemical Methods)
Section cross-reference(s): 1
- ST drug screening **modulation** activity **PIPKI cell migration** mediated disease; **phosphatidylinositol phosphate kinase modulation** drug screening
- IT Disease, animal
(**cell migration** associated; methods for identifying agents **modulating** activity of **PIPKI.gamma.661** for preventing or treating **cell-migration** mediated conditions or diseases)
- IT Cell junction
(focal contact, **modulation** of; methods for identifying agents **modulating** activity of **PIPKI.gamma.661** for preventing or treating **cell-migration** mediated conditions or diseases)
- IT **Cell migration**
Drug screening
Molecular cloning
(methods for identifying agents **modulating** activity of **PIPKI.gamma.661** for preventing or treating **cell-migration** mediated conditions or diseases)
- IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p125FAK; methods for identifying agents **modulating** activity of **PIPKI.gamma.661** for preventing or treating **cell-migration** mediated conditions or diseases)
- IT 141349-89-5, **SRC** kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(methods for identifying agents **modulating** activity of **PIPKI.gamma.661** for preventing or treating **cell-migration** mediated conditions or diseases)
- IT 59977-48-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type I, isoform .gamma.661; methods for identifying agents **modulating** activity of **PIPKI.gamma.661** for preventing or treating **cell-migration** mediated conditions or diseases)
- IT 818384-78-0 818384-79-1 818384-80-4 818384-81-5 818384-82-6
818384-83-7 818384-84-8 818384-85-9 818384-86-0
RL: PRP (Properties)
(unclaimed nucleotide sequence; methods for identifying agents

modulating activity of **PIPKI.gamma.661** for preventing or treating **cell-migration** mediated conditions or diseases)

IT 818384-69-9 818384-70-2 818384-71-3 818384-72-4 818384-73-5
818384-74-6 818384-75-7 818384-76-8 818384-77-9 818384-87-1
818384-88-2 818384-89-3 818384-90-6 818384-91-7 818384-92-8

RL: PRP (Properties)

(unclaimed protein sequence; methods for identifying agents **modulating** activity of **PIPKI.gamma.661** for preventing or treating **cell-migration** mediated conditions or diseases)

IT 208183-74-8 818377-04-7 818377-05-8 818377-06-9 818377-07-0

RL: PRP (Properties)

(unclaimed sequence; methods for identifying agents **modulating** activity of **PIPKI.gamma.661** for preventing or treating **cell-migration** mediated conditions or diseases)

L14 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:771070 CAPLUS

DOCUMENT NUMBER: 139:347262

TITLE: The C-terminal Domain of Rac1 Contains Two Motifs That Control Targeting and Signaling Specificity

AUTHOR(S): van Hennik, Paula B.; ten Klooster, Jean Paul; Halstead, Jon R.; Voermans, Carlijn; Anthony, Eloise C.; Divecha, Nullin; Hordijk, Peter L.

CORPORATE SOURCE: Academic Medical Center, Sanquin Research at CLB and Landsteiner Laboratory, University of Amsterdam, Amsterdam, 1066 CX, Neth.

SOURCE: Journal of Biological Chemistry (2003), 278(40), 39166-39175

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 02 Oct 2003

AB Rho-like GTPases control a wide range of cellular functions such as integrin- and cadherin-mediated **adhesion**, cell motility, and gene expression. The hypervariable C-terminal domain of these GTPases has been implicated in membrane association and effector binding. We found that cell-permeable peptides, encoding the C termini of Rac1, Rac2, RhoA, and Cdc42, interfere with GTPase signaling in a specific fashion in a variety of cellular models. Pull-down assays showed that the C terminus of Rac1 does not associate to either RhoGDI or to Pak. In contrast, the C terminus of Rac1 (but not Rac2 or Cdc42) binds to phosphatidylinositol 4,5-phosphate kinase (PIP5K) via amino acids 185-187 (RKR). Moreover, Rac1 assoc. to the adapter protein Crk via the N-terminal **Src** homol. 3 (SH3) domain of Crk and the proline-rich stretch in the Rac1 C terminus. These differential interactions mediate Rac1 localization, as well as Rac1 signaling, toward membrane ruffling, **cell-cell adhesion**, and **migration**. These data show that the C-terminal, hypervariable domain of Rac1 encodes two distinct binding motifs for signaling proteins and regulates intracellular targeting and differential signaling in a unique and non-redundant fashion.

CC 6-3 (General Biochemistry)

ST Rac1 protein motif signal transduction binding **phosphatidylinositol phosphate kinase**; Crk SH3 domain binding Rac1 **phosphatidylinositol phosphate**

kinase

IT **Adhesion**, biological

Signal transduction, biological

(C-terminal domain of Rac1 assoc. with effector and adapter proteins
to regulate targeting and signaling specificity)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 16 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2004143283 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15037311
TITLE: Talin: an emerging focal point of **adhesion**
dynamics.
AUTHOR: Nayal Anjana; Webb Donna J; Horwitz Alan F
CORPORATE SOURCE: Department of Cell Biology, UVa School of Medicine, 1300
Jefferson Park Ave, PO Box 800732, Charlottesville, VA
22908-0732, USA.
SOURCE: Current opinion in cell biology, (2004 Feb) 16 (1) 94-8.
Ref: 50
Journal code: 8913428. ISSN: 0955-0674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200410
ENTRY DATE: Entered STN: 20040324
Last Updated on STN: 20041015
Entered Medline: 20041014
AB The **adhesion** protein talin and the phosphoinositide PIP2 are
emerging as key **modulators** of **adhesion** dynamics.
Recent genetic studies on talin demonstrate its physiological role in
organizing **adhesions**, stabilizing integrin-actin linkages and
mediating integrin signaling in vivo. Biophysical force measurements
provide further evidence that it is required for the reinforcement of the
extracellular matrix-integrin-actin connection. Knockdown data along with
structural analyses establish a major role for talin in 'inside-out'
integrin activation through its direct interaction with integrin
cytoplasmic domains. A recently uncovered role for talin is the
recruitment of a **PIPKI gamma** isoform to
adhesions. This introduces a novel connection between talin and
PIP2 generation. Finally, PIP2 also stimulates the transient, direct
binding interaction of the Arp2/3 complex with vinculin and thus may
couple **adhesion** to actin assembly.
CT Animals
*Cell Adhesion
*Cell Adhesion Molecules: ME, metabolism
Cell Movement
Integrins: ME, metabolism
Phosphatidylinositol 4,5-Diphosphate: BI, biosynthesis
*Talin: PH, physiology
L14 ANSWER 10 OF 16 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights
reserved on STN
ACCESSION NUMBER: 2004300117 EMBASE
TITLE: Competition for talin results in trans-dominant inhibition

of integrin activation.
 AUTHOR: Calderwood D.A.; Tai V.; Di Paolo G.; De Camilli P.;
 Ginsberg M.H.
 CORPORATE SOURCE: D.A. Calderwood, Department of Cell Biology, Scripps
 Research Institute, San Diego, CA 92037, United States.
 david.calderwood@ale.edu
 SOURCE: Journal of Biological Chemistry, (9 Jul 2004) Vol. 279, No.
 28, pp. 28889-28895.
 Refs: 65
 ISSN: 0021-9258 CODEN: JBCHA3
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 029 Clinical Biochemistry
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ENTRY DATE: Entered STN: 20040805
 Last Updated on STN: 20040805

AB The ability of integrin **adhesion** receptors to undergo rapid
 changes in affinity for their extracellular ligands (integrin activation)
 is essential for the development and function of multicellular animals and
 is dependent on interactions between the integrin β
 subunit-cytoplasmic tail and the cytoskeletal protein talin. Cross-talk
 among different integrins and between integrins and other receptors
 impacts many cellular processes including **adhesion**, spreading,
 migration, clot retraction, proliferation, and differentiation. One form
 of integrin cross-talk, transdominant inhibition of integrin activation,
 occurs when ligand binding to one integrin inhibits the activation of a
 second integrin. This may be relevant clinically in a number of settings
 such as during platelet **adhesion**, leukocyte trans-migration, and
 angiogenesis. Here we report that competition for talin underlies the
 trans-dominant inhibition of integrin activation. This conclusion is
 based on our observations that (i) β tails selectively defective in
 talin binding are unable to mediate trans-dominant inhibition, (ii)
 trans-dominant inhibition can be reversed by overexpression of integrin
 binding and activating fragments of talin, and (iii) expression of another
 non-integrin talin-binding protein, **phosphatidylinositol**
phosphate kinase type I γ -90, also inhibits
 integrin activation. Thus, the sequestration of talin by the suppressive
 species is both necessary and sufficient for trans-dominant inhibition of
 integrin activation.

CT Medical Descriptors:
 *protein binding
 *binding competition
 *signal transduction
 *transdominant integrin activation inhibition
 receptor affinity
 protein protein interaction
 cell adhesion
 cell spreading
 cell migration
 blood clot retraction
 cell proliferation
 cell differentiation
 ligand binding
 thrombocyte adhesion
 leukocyte migration
 angiogenesis
 gene overexpression
 nonhuman
 animal cell

article
nucleotide sequence
priority journal
Drug Descriptors:
*talin
*integrin
integrin receptor
ligand
protein subunit
cytoskeleton protein
peptide fragment
binding protein
talin binding protein
phosphatidylinositol 4 phosphate kinase
phosphatidylinositol 4 phosphate kinase type Igamma 90
unclassified drug

L14 ANSWER 11 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on
STN

ACCESSION NUMBER: 2005:396518 BIOSIS

DOCUMENT NUMBER: PREV200510186550

TITLE: Focal **adhesion** targeting of PIPKIgamma661
requires tyrosine phosphorylation of by **Src** and
regulates an integrin-talin switch.

AUTHOR(S): Ling, Kun [Reprint Author]; Doughman, Renee L.; Firestone,
Ari J.; Anderson, Richard

CORPORATE SOURCE: Univ Wisconsin, Dept Pharmacol, Madison, WI 53706 USA

SOURCE: FASEB Journal, (MAY 14 2004) Vol. 18, No. 8, Suppl. S, pp.
C314.

Meeting Info.: Annual Meeting of the American-Society-for-
Biochemistry-and-Molecular-Biology/8th Congress of the
International-Union-for-Biochemistry-and-Molecular-Biology.
Boston, MA, USA. June 12 -16, 2004. Amer Soc BioChem & Mol
Biol; Int Union Biochem & Mol Biol.

CODEN: FAJOEC. ISSN: 0892-6638.

DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 5 Oct 2005

Last Updated on STN: 5 Oct 2005

AB Cell adherence to the extracellular matrix, is dependent on integrin
assembly of focal **adhesions**. Phosphatidylinositol-4,5-
bisphosphate (PtdIns(4,5)P₂) regulates interactions between these
proteins, including the interaction of vinculin with actin and talin. The
binding of talin to beta-integrin is strengthened by PtdIns(4,5)P₂,
suggesting that the basis of focal **adhesion** assembly is
regulated by this lipid mediator. Here we show that the type I
phosphatidylinositol phosphate kinase isoform-**gamma** 661 (
PIPKI gamma 661), an enzyme that makes PtdIns(4,5)P₂, is
targeted to focal **adhesions** by an association with talin.
PIPKI gamma 661 is tyrosine phosphorylated by focal
adhesion associated kinase signalling, increasing both the
activity of phosphatidylinositol phosphate kinase and its association with
talin. The tyrosine phosphorylation of **PIPKI gamma**
661 on tyrosine 644 (Y644) is critical for its interaction with talin, and
consequently, localization to FAs. **PIPKI gamma** 661 is
specifically phosphorylated on Y644 by **Src** and this
phosphorylation is regulated by focal **adhesion** kinase, which
enhances an association between **PIPKI gamma** 661 and
Src. The phosphorylation of Y644 results in a 15-fold increase in

binding affinity to the talin head domain and competes with integrin binding to talin. This defines a novel phosphotyrosine-binding site on the talin F3 domain and a "molecular switch" for talin binding between **PIPKI gamma 661** and P-integrin that may regulate dynamic FA turnover. Supported by the NIH.

IT Major Concepts

Enzymology (Biochemistry and Molecular Biophysics); Cell Biology

IT Chemicals & Biochemicals

focal **adhesion** kinase [EC 2.7.1.112]; **Src**; tyrosine; phosphatidylinositol-4,5-bisphosphate; beta-integrin; integrin; talin; focal **adhesion** protein; phosphatidylinositol phosphate kinase; type I phosphatidylinositol phosphate kinase isoform-gamma-661 [PIPKIgamma661]

L14 ANSWER 12 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:396265 BIOSIS

DOCUMENT NUMBER: PREV200510186297

TITLE: Type I gamma phosphatidylinositol phosphate kinase directly interacts with and is a substrate for Shp-1 tyrosine phosphatase.

AUTHOR(S): Bairstow, Shawn [Reprint Author]; Ling, Kun; Anderson, Richard

CORPORATE SOURCE: Univ Wisconsin, Dept Biomol Chem, Madison, WI 53706 USA

SOURCE: FASEB Journal, (MAY 14 2004) Vol. 18, No. 8, Suppl. S, pp. C259.

Meeting Info.: Annual Meeting of the American-Society-for-Biochemistry-and-Molecular-Biology/8th Congress of the International-Union-for-Biochemistry-and-Molecular-Biology. Boston, MA, USA. June 12 -16, 2004. Amer Soc BioChem & Mol Biol; Int Union Biochem & Mol Biol. CODEN: FAJOEC. ISSN: 0892-6638.

DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 5 Oct 2005

Last Updated on STN: 5 Oct 2005

AB Tyrosine phosphorylation plays a critical role in several regulatory aspects of cellular signaling. Dephosphorylation of these residues is crucial for termination of signals initiated by tyrosine kinases. Previous work in our laboratory has shown that the tyrosine kinase **Src** phosphorylates Y644 on type I **gamma** phosphatidylinositol phosphate kinase (**PIPKI gamma 661**) in a focal **adhesion** kinase (**FAK**) dependent manner. Phosphorylation of this residue is key for high affinity binding of **PIPKI gamma 661** to the focal **adhesion** protein talin and fortargeting of **PIPKI gamma 661** to focal **adhesions** at the plasma membrane. A yeast 2-hybrid screen performed with the C-terminal 178 amino acid tail of **PIPKI gamma 661** identified an interaction with the phosphatase domain of the tyrosine phosphatase Shp-1. We have subsequently shown that Shp-1 directly interacts with **PIPKI gamma 661**. In addition, we have evidence demonstrating that phosphorylated **PIPKI gamma 661** can serve as a substrate for Shp-1 via in vitro phosphatase assays. Shp-1 phosphatase assays have also indicated that phosphatidylinositol 4,5-bisphosphate may be an important regulator of Shp- I phosphatase activity. Finally, we have also examined the impact of Shp-1 mediated dephosphorylation on the association between **PIPKI gamma 661** and talin and targeting of **PIPKI gamma 661** to focal **adhesions**.

IT Major Concepts
 Biochemistry and Molecular Biophysics; Cell Biology
 IT Parts, Structures, & Systems of Organisms
 plasma membrane
 IT Chemicals & Biochemicals
 focal **adhesion** kinase [EC 2.7.1.112]; talin; tyrosine kinase
Src; type-I-gamma phosphatidylinositol phosphate kinase:
 phosphorylation; Shp-1 tyrosine phosphatase

L14 ANSWER 13 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on
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ACCESSION NUMBER: 2005:396267 BIOSIS

DOCUMENT NUMBER: PREV200510186299

TITLE: Tyrosine Phosphorylation of Type I gamma
phosphatidylinositol phosphate
kinase by Src regulates an integrin-talin
 switch.

AUTHOR(S): Ling, Kun [Reprint Author]; Doughman, R. L.; Iyer, V. V.;
 Firestone, A. J.; Bairstow, S. F.; Mosher, D. F.; Schaller,
 M. D.; Anderson, R. A.

CORPORATE SOURCE: Univ N Carolina, Dept Cell and Dev Biol, Chapel Hill, NC
 27599 USA

SOURCE: FASEB Journal, (MAY 14 2004) Vol. 18, No. 8, Suppl. S, pp.
 C259-C260.
 Meeting Info.: Annual Meeting of the American-Society-for-
 Biochemistry-and-Molecular-Biology/8th Congress of the
 International-Union-for-Biochemistry-and-Molecular-Biology.
 Boston, MA, USA. June 12 -16, 2004. Amer Soc BioChem & Mol
 Biol; Int Union Biochem & Mol Biol.
 CODEN: FAJOEC. ISSN: 0892-6638.

DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 5 Oct 2005

Last Updated on STN: 5 Oct 2005

AB Engagement of integrin receptors with the extracellular matrix induces the
 formation of focal **adhesions** (FAs). Dynamic regulation of FAs
 is necessary for **cells** to polarize and **migrate**. Key
 interactions between FA scaffolding and signaling proteins are dependent
 upon tyrosine phosphorylation. However, the precise role of tyrosine
 phosphorylation in FA development and maturation is poorly defined. Here
 we show that phosphorylation of type I gamma **phosphatidylinositol**
phosphate kinase (PIPKI gamma 661)
 on tyrosine 644 (Y644) is critical for its interaction with talin and
 consequently localization to FAs. PIPKI gamma 661 is specifically
 phosphorylated on Y644 by **Src**. Phosphorylation is regulated by
FAK which enhances the association between PIPKI gamma
661 and **Src**. The phosphorylation of Y644 results in
 similar to 15-fold increase in binding affinity to the talin head domain
 and blocks beta-integrin binding to talin. This defines a novel
 phosphotyrosine binding site on the talin F3 domain and a 'molecular
 switch' for talin binding between PIPKI gamma 661 and
 beta-integrin that regulates the generation of PI4,5P(2) at FAs and may
 regulate dynamic FA turnover.

IT Major Concepts
 Biochemistry and Molecular Biophysics; Cell Biology
 IT Parts, Structures, & Systems of Organisms
 extracellular matrix
 IT Chemicals & Biochemicals
 signaling proteins; **Src**; beta-integrin; integrin; integrin

receptors; **FAK**; talin; P14 protein; type-I-gamma-
phosphatidylinositol phosphate kinase:
phosphorylation; phosphotyrosine binding site

L14 ANSWER 14 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on
STN

ACCESSION NUMBER: 2005:395646 BIOSIS

DOCUMENT NUMBER: PREV200510185678

TITLE: Nuclear phosphatidylinositol-4,5 bisphosphate generation
regulates the assembly of splicing factor speckles and
splicing of pre-mRNA.

AUTHOR(S): Song, Chunhua [Reprint Author]; Gonzales, Michael L.;
Anderson, Richard A.

CORPORATE SOURCE: Univ Wisconsin, Sch Med, Dept Pharmacol, Madison, WI 53706
USA

SOURCE: FASEB Journal, (MAY 14 2004) Vol. 18, No. 8, Suppl. S, pp.
C124.
Meeting Info.: Annual Meeting of the American-Society-for-
Biochemistry-and-Molecular-Biology/8th Congress of the
International-Union-for-Biochemistry-and-Molecular-Biology.
Boston, MA, USA. June 12 -16, 2004. Amer Soc BioChem & Mol
Biol; Int Union Biochem & Mol Biol.
CODEN: FAJOEC. ISSN: 0892-6638.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 5 Oct 2005

Last Updated on STN: 5 Oct 2005

AB In mammals, there are three Phosphatidylinositol-phosphate Kinase type I
(PIPK1) isoforms: PIPKI alpha, **PIPKI** beta, and **PIPKI**
gamma. These isoforms each localize to distinct intracellular
compartments, suggesting they **modulate** different functions. We
have shown that PIPKI alpha and Phosphatidylinositol-4,5 bisphosphate
(PI4,5P(2)) generation co-localize with splicing factors innuclear
speckles. Nuclear speckles, also called splicing factor compartments,are
"depots" which harbor splicing factors and are associated with sites for
active gene transcription and processing. Splicing factors translocate
from these "depots" to sites of active gene transcription by mechanisms
that are not yet understood. Here we show that PIPKI alpha is the major
enzyme responsible for the synthesis of PI4,5P(2) in the nucleus.
Furthermore we show that this nuclear PI4,5P(2) is responsible for
maintaining splicing factors in nuclear speckles by regulating their
phosphorylation. Finally we show that changes in splicing factor
phosphorylation caused by **modulating** nuclear PI4,5P(2) levels
can affect pre-mRNA splicing. Combined, these resultsdemonstrate that
PIPKI alpha and PI4,5P(2) play a critical role in maintenance of splicing
machinery organization and regulation of alternative pre-mRNA splicing.

IT Major Concepts

Enzymology (Biochemistry and Molecular Biophysics); Cell Biology

IT Parts, Structures, & Systems of Organisms
nucleus

IT Chemicals & Biochemicals

splicing factor; phosphatidylinositol-4,5-biphosphate; pre-messenger
RNA [pre-mRNA]; phosphatidylinositol-phosphate kinase type I isoform;
phosphatidylinositol-phosphate kinase type I-alpha [PIPKI-alpha];
phosphatidylinositol-phosphate kinase type I-beta [PIPKI-beta];
phosphatidylinositol-phosphate kinase type I-**gamma** [
PIPKI-gamma]; gene: transcription, processing

L14 ANSWER 15 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on

STN

ACCESSION NUMBER: 2003:149603 BIOSIS
 DOCUMENT NUMBER: PREV200300149603
 TITLE: Cell **adhesion**: A FERM grasp of membrane dynamics.
 AUTHOR(S): Liddington, Robert C. [Reprint Author]; Bankston, Laurie A. [Reprint Author]; de Pereda, Jose M. [Reprint Author]
 CORPORATE SOURCE: Program on Cell Adhesion, The Burnham Institute, 10901 North Torrey Pines Road, La Jolla, CA, 92037, USA
 rliddington@burnham.org
 SOURCE: Current Biology, (February 4 2003) Vol. 13, No. 3, pp. R94-R95. print.
 ISSN: 0960-9822 (ISSN print).
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 19 Mar 2003
 Last Updated on STN: 19 Mar 2003

AB Two recent papers provide the first evidence for a common mechanism of targeting and activation of an enzyme that is important in the rapid regulation of both focal **adhesion** assembly during **cell migration** and synaptic vesicle recycling at nerve terminals.

IT Major Concepts

Enzymology (Biochemistry and Molecular Biophysics); Membranes (Cell Biology); Nervous System (Neural Coordination)

IT Parts, Structures, & Systems of Organisms

brain: nervous system; focal **adhesion**; membrane, dynamics; nerve terminal: nervous system; synaptic vesicle: nervous system

IT Chemicals & Biochemicals

focal **adhesion** kinase [EC 2.7.1.112]; integrin; integrin-beta; **phosphatidylinositol phosphate kinase** type 1-gamma; talin: FERM domain; vinculin

L14 ANSWER 16 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:391924 BIOSIS
 DOCUMENT NUMBER: PREV200300391924
 TITLE: Type Igamma phosphatidylinositol phosphate kinase targets to and regulates focal **adhesions**.
 AUTHOR(S): Doughman, Renee L. [Reprint Author]; Ling, Kun; Firestone, Ari J.; Bunce, Matthew W.; Anderson, Richard A.
 CORPORATE SOURCE: Pharmacology, University of Wisconsin-Madison, 1300 University Ave, Madison, WI, 53706, USA
 rldierckman@wisc.edu; kunling@wisc.edu; ajfirestone@wisc.edu; mwBunce@wisc.edu; raanders@wisc.edu
 SOURCE: FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 628.1. <http://www.fasebj.org/>. e-file.
 Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. San Diego, CA, USA. April 11-15, 2003. FASEB.
 ISSN: 0892-6638 (ISSN print).
 DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 27 Aug 2003
 Last Updated on STN: 27 Aug 2003

AB The ability of cells to form cell contacts, adhere to the extracellular matrix, change morphology, and migrate are events essential for development, wound healing, metastasis, cell survival, and the immune response. These events are dependent upon integrin binding to the extracellular matrix and assembly of focal **adhesions**. Focal **adhesions** are complexes comprised of scaffolding and signaling

proteins organized by **adhesion** to the extracellular matrix. Phosphatidylinositol-4,5-bisphosphate (PI4,5P2) regulates interactions between these proteins, including the interaction of vinculin with actin and talin. The binding of talin to α -integrin is strengthened by PI4,5P2, suggesting that the basis of focal **adhesion** assembly is regulated by this lipid mediator. Here we show that the type I phosphatidylinositol phosphate kinase **gamma** (PIPKI (661), an enzyme that makes PI4,5P2, is targeted to focal **adhesions** by an association with talin. PIPKI(661 is tyrosine phosphorylated by focal **adhesion** associated kinase (FAK) signaling, increasing both PIP kinase activity and association with talin. This defines a mechanism for spatial generation of PI4,5P2 at focal **adhesions**.

- IT Major Concepts
 - Enzymology (Biochemistry and Molecular Biophysics)
- IT Parts, Structures, & Systems of Organisms
 - extracellular matrix; focal **adhesions**
- IT Chemicals & Biochemicals
 - actin; focal **adhesion** kinase [EC 2.7.1.112]: signaling;
 - phosphatidylinositol-4,5-bisphosphate; talin; type 1
 - phosphatidylinositol phosphate-gamma; vinculin

=> □

=> d que l25

L1 13 SEA (PIPKI OR PIPK) (3A) 661
 L2 458 SEA PHOSPHATIDYLINOSITOL PHOSPHATE (2W) KINASE
 L3 16 SEA L2 AND 661
 L4 16 SEA L1 OR L3
 L5 133994 SEA CELL (3A) MIGRAT?
 L6 7 SEA L4 AND L5
 L7 24 SEA L2 AND L5
 L8 14 SEA L7 AND (SRC OR FAK OR MODULAT? OR ADHESI?)
 L9 14 SEA L6 OR L8
 L10 9 DUP REM L9 (5 DUPLICATES REMOVED)
 L11 37 SEA (PIPKI OR PIPK) (3A) GAMMA
 L12 23 SEA L11 AND (SRC OR FAK OR MODULAT? OR ADHESI?)
 L13 18 SEA L12 NOT L10
 L14 16 DUP REM L13 L10 (11 DUPLICATES REMOVED)
 L15 25867 SEA ANDERSON R?/AU
 L16 950 SEA LING K?/AU
 L17 21 SEA DOUGHMAN R?/AU
 L18 26801 SEA (L15 OR L16 OR L17)
 L19 74 SEA L18 AND (L1 OR L2 OR L11)
 L20 14 SEA L19 AND (L1 OR L11)
 L21 74 SEA L18 AND L2
 L22 26 SEA L21 AND (SRC OR FAK OR MODULAT? OR ADHES?)
 L23 26 SEA L20 OR L22
 L24 13 DUP REM L23 (13 DUPLICATES REMOVED)
 L25 3 SEA L24 NOT L14

=> d ibib ca ct l25 1-3

'CA' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'
 ENTER DISPLAY FORMAT (BIB):end

=> d ibib ab ct l25 1-3

L25 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2003:709891 CAPLUS
 DOCUMENT NUMBER: 139:392716
 TITLE: **Phosphatidylinositol phosphate kinases** put PI4,5P2 in its place
 AUTHOR(S): **Doughman, R. L.**; Firestone, A. J.; **Anderson, R. A.**
 CORPORATE SOURCE: Molecular and Cellular Pharmacology Program,
 Department of Pharmacology, University of
 Wisconsin-Madison, Madison, WI, 53706, USA
 SOURCE: Journal of Membrane Biology (2003), 194(2), 77-89
 CODEN: JMBBBO; ISSN: 0022-2631
 PUBLISHER: Springer-Verlag New York Inc.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review. Phosphatidylinositol 4,5-bisphosphate (PI4,5P2) is a critical 2nd messenger that regulates a myriad of diverse cellular activities including **modulation** of the actin cytoskeleton, vesicle trafficking, focal **adhesion** formation, and nuclear events. In order to effectively regulate these disparate cellular events, the biosynthesis of PI4,5P2 by **phosphatidylinositol phosphate kinases** (PIP kinases) must be both spatially and temporally regulated. Two subfamilies of PIP kinases, types I and II, allow the generation of PI4,5P2 from independent pools of substrate, PI(4)P and PI(5)P resp. In turn, type I and II PIP kinases show different subcellular localization

and thus are involved in distinct signaling pathways. Addnl., several type I isoforms, and their splice variants, have now been shown to be differentially localized throughout the cell and to be involved in the synthesis of PI4,5P2 at distinct sites. These findings implicate PIP kinases as the major regulators of PI4,5P2-mediated events, making them key signaling enzymes in a variety of processes. Understanding the mechanisms regulating spatial and temporal biosynthesis of PI4,5P2 by PIP kinases is vital for understanding these processes as a whole. This review examines both structural and regulatory features that **modulate** activity, localization, and substrate usage of PIPKs.

CT Signal transduction, biological

CT Phosphatidylinositol 4,5-bisphosphate

REFERENCE COUNT: 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:862702 CAPLUS

DOCUMENT NUMBER: 138:302408

TITLE: Inhibition of Phosphatidylinositol-4-phosphate 5-Kinase Ialpha Impairs Localized Actin Remodeling and Suppresses Phagocytosis

AUTHOR(S): Coppolino, Marc G.; Dierckman, Renee; Loijens, Joost; Collins, Richard F.; Pouladi, Mahmoud; Jongstra-Bilen, Jenny; Schreiber, Alan D.; Trimble, William S.; **Anderson, Richard**; Grinstein, Sergio

CORPORATE SOURCE: Department of Biochemistry, University of Toronto, Hospital for Sick Children, Cell Biology Program, ON, M5G 1X8, Can.

SOURCE: Journal of Biological Chemistry (2002), 277(46), 43849-43857

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Actin polymerization drives the extension of pseudopods required for phagocytosis. Phosphatidylinositol 4,5-bisphosphate (PIP2) is thought to play a central role in this process, because it interacts with several actin-regulatory proteins and undergoes acute and localized changes at sites of phagocytosis. The authors therefore studied whether phosphatidylinositol-4-phosphate 5-kinase (PIP5K), the enzyme responsible for the generation of PIP2 from phosphatidylinositol 4-phosphate, is involved in the control of phagocytosis. PIP5K α was found to accumulate transiently on forming phagosomes. To test the functional involvement of PIP5K α in particle engulfment, the authors generated a double mutant (D309N/R427Q) that lacks kinase activity. When ectopically expressed in cultured cells, this mutant is targeted to the plasma membrane and accumulates at the phagosomal cup during particle engulfment. Expression of PIP5K α D309N/R427Q impaired phagocytosis in RAW264.7 macrophages and in engineered phagocytes generated by transfection of Fc receptors in Chinese hamster ovary cells. Inhibition of phagocytosis could not be attributed to defects in particle binding or receptor clustering, which was monitored using green fluorescent protein-tagged Fc γ receptors. Instead, expression of the inactive kinase diminished the accumulation of PIP2 and of F-actin in the phagosomal cup. Thus, PIP5K α activity is involved in the actin remodeling that is a prerequisite for efficient phagocytosis. PIP5K α appears to contribute to the transient changes in PIP2 levels that are associated with, and likely required for, the recruitment and regulation of actin-**modulating** proteins.

CT Actins
 CT Phagocytosis
 CT Phosphatidylinositol 4,5-bisphosphate
 CT Phosphatidylinositol 4-phosphate
 CT Macrophage
 CT Actins

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1990:607217 CAPLUS

DOCUMENT NUMBER: 113:207217

TITLE: The human erythrocyte contains two forms of
 phosphatidylinositol-4-phosphate 5-kinase which are
 differentially active toward membranes

AUTHOR(S): Bazenet, Chantal E.; Ruiz Ruano, Antonio; Brockman,
 Jennifer L.; **Anderson, Richard A.**

CORPORATE SOURCE: Med. Sch., Univ. Wisconsin, Madison, WI, 53706, USA

SOURCE: Journal of Biological Chemistry (1990), 265(29),
 18012-22

CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A human erythrocyte cytosolic phosphatidylinositol-4-phosphate 5-kinase
 (PIP kinase) and a membrane-bound PIP kinase have been purified by
 phosphocellulose chromatog. Fractionation of the membrane-bound PIP
 kinase activities by phosphocellulose separated activity into two peaks, which
 eluted at 0.6 M NaCl (type I PIP kinase) and 1.0M NaCl (type II PIP
 kinase). The cytosolic PIP kinase and the membrane-bound type II PIP
 kinase are 53 kDa by SDS-PAGE, have indistinguishable 125I-peptide maps,
 and are immunochem. indistinguishable, suggesting that they are sequence
 identical. Antibodies raised to the cytosolic PIP kinase inhibit activity
 of both the membrane-bound type II and the cytosolic PIP kinases. The
 type I PIP kinase appears to be distinct from the cytosolic and
 membrane-bound type II PIP kinase; it is not immunocross-reactive, and
 antibodies toward type II PIP kinases do not inhibit type I PIP kinase.
 Further, membrane-bound type II PIP kinase can be removed from type I PIP
 kinase without loss of activity. Functional characterization of the PIP
 kinases demonstrates that the type I kinase has a 10-fold lower Km for PIP
 and a 5-fold higher Km for ATP compared with the type II enzymes. The
 type I and type II (membrane-bound or cytosolic) PIP kinases are
modulated differentially by spermine and heparin. Finally, the
 type I PIP kinase phosphorylates intrinsic PIP on isolated erythrocyte
 membranes, whereas the type II PIP kinases have no activity toward native
 membranes.

CT Michaelis constant
 CT Erythrocyte
 CT Membrane, biological
 CT Cytoplasm
 CT Phosphoinositides

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